



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/255, 31/35, 31/7048, A61P 3/04		A1	(11) International Publication Number: WO 00/61140
			(43) International Publication Date: 19 October 2000 (19.10.00)
(21) International Application Number: PCT/US00/08442			(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 30 March 2000 (30.03.00)			
(30) Priority Data: 60/128,348 8 April 1999 (08.04.99) US 09/538,814 30 March 2000 (30.03.00) US			
(71) Applicant: ORTHO-MCNEIL PHARMACEUTICAL, INC. [US/US]; U.S. Route #202, P.O. Box 300, Raritan, NJ 08869-0602 (US).			
(72) Inventor: KAMIN, Marc; 33 Lorrie Lane, Lawrenceville, NJ 08646 (US).			
(74) Agents: CIAMPORCERO, Audley, A., Jr. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933 (US).			Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: ANTICONVULSANT DERIVATIVES USEFUL IN MAINTAINING WEIGHT LOSS			
(57) Abstract Use of anticonvulsant derivatives of formula I for maintaining weight loss wherein X is CH ₂ or oxygen; R ₁ is hydrogen or alkyl; and R ₂ , R ₃ , R ₄ and R ₅ are independently hydrogen or alkyl and, when X is CH ₂ , R ₄ and R ₅ may be alkene groups joined to form a benzene ring and, when X is oxygene, R ₂ and R ₃ and/or R ₄ and R ₅ together may be a methylenedioxy group of formula (II) wherein R ₆ and R ₇ are the same or different and are hydrogen or alkyl and are joined to form a cyclopentyl or cyclohexyl ring.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

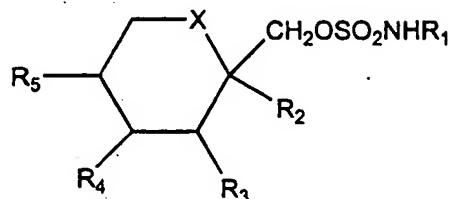
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

ANTICONVULSANT DERIVATIVES USEFUL IN MAINTAINING WEIGHT LOSS

BACKGROUND OF THE INVENTION

5

Compounds of Formula I:



are structurally novel antiepileptic compounds that are highly effective anticonvulsants in animal tests (Maryanoff, B.E, Nortey, S.O., Gardocki, J.F., Shank, R.P. and Dodgson, S.P. *J. Med. Chem.* 30, 880-887, 1987; Maryanoff, B.E., Costanzo, M.J., Shank, R.P., Schupsky, J.J., Ortegon, M.E., and Vaught J.L. *Bioorganic & Medicinal Chemistry Letters* 3, 2653-2656, 1993). These compounds are covered by US Patent No.4,513,006. One of these compounds 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate known as topiramate has been demonstrated in clinical trials of human epilepsy to be effective as adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. FAUGHT, B.J. WILDER, R.E. RAMSEY, R.A. REIFE, L D. KRAMER, G.W. PLEDGER, R.M. KARIM et. al., *Epilepsia* 36 (S4) 33, 1995; S.K. SACHDEO, R.C. SACHDEO, R.A. REIFE, P. LIM and G. PLEDGER, *Epilepsia* 36 (S4) 33, 1995), and is currently marketed for the treatment of simple and complex partial seizure epilepsy with or without secondary generalized seizures in approximately twenty countries including the United States, and applications for regulatory approval are presently pending in several additional countries throughout the world.

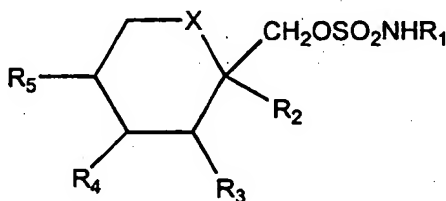
Compounds of Formula I were initially found to possess anticonvulsant activity in the traditional maximal electroshock seizure (MES) test in mice (SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O., and MARYANOFF, B.E., *Epilepsia* 35 450-460, 1994). Subsequent studies revealed that Compounds of Formula I were also highly

effective in the MES test in rats. More recently topiramate was found to effectively block seizures in several rodent models of epilepsy (J. NAKAMURA, S. TAMURA, T. KANDA, A. ISHII, K. ISHIHARA, T. SERIKAWA, J. YAMADA, and M. SASA, Eur. J. Pharmacol. 254 83-89, 1994), and in an animal model of kindled epilepsy (A. WAUQUIER and S. ZHOU, Epilepsy Res. 24, 73-77, 1996). Even more recently, topiramate has been found to effectively reduce the weight in overweight individuals. (U.S. Patent Application # 08/881,009.)

Clinical studies on topiramate have revealed previously unrecognized pharmacological properties which suggest that topiramate will be effective in maintaining weight loss in individuals who have lost weight by one or more means.

DISCLOSURE OF THE INVENTION

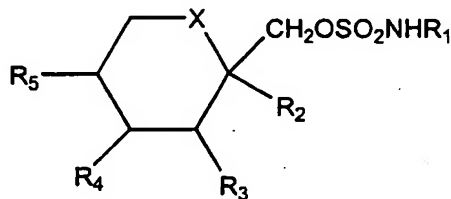
Accordingly, it has been found that compounds of the following formula I:



wherein X is O or CH₂, and R₁, R₂, R₃, R₄ and R₅ are as defined hereinafter are useful in maintaining weight loss.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIEMENTS

The sulfamates of the invention are of the following formula (I):



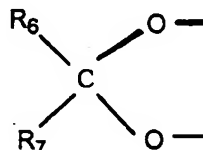
wherein

X is CH₂ or oxygen;

R₁ is hydrogen or alkyl; and

R₂, R₃, R₄ and R₅ are independently hydrogen or alkyl and, when X is CH₂, R₄ and R₅ may be alkene groups joined to form a benzene ring and, when X is oxygen, R₂ and

- 5 R₃ and/or R₄ and R₅ together may be a methylenedioxy group of the following formula (II):



wherein

- 10 R₆ and R₇ are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

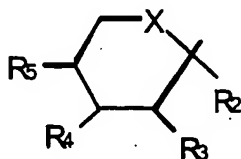
- R₁ in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl and iso-propyl. Alkyl throughout this specification includes straight and branched chain alkyl. Alkyl groups for R₂, R₃, R₄, R₅, R₆ and R₇ are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl. When X is CH₂, R₄ and R₅ may combine to form a benzene ring fused to the 6-membered X-containing ring, i.e., R₄ and R₅ are defined by the alkatrienyl group =C-CH=CH-CH=.
- 15

- A particular group of compounds of formula (I) is that wherein X is oxygen and both R₂ and R₃ and R₄ and R₅ together are methylenedioxy groups of the formula (II), wherein R₆ and R₇ are both hydrogen both alkyl or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where R₆ and R₇ are both alkyl such as methyl. A second group of compounds is that wherein X is CH₂ and R₄ and R₅ are joined to form a benzene ring. A third group of compounds of formula (I) is that wherein both R₂ and R₃ are hydrogen.
- 20

- 25 The compounds of formula (I) may be synthesized by the following methods:

(a) Reaction of an alcohol of the formula RCH₂OH with a chlorosulfamate of the formula ClSO₂NH₂ or ClSO₂NHR₁ in the presence of a base such as potassium *n*-butoxide or sodium hydride at a temperature of about -20° to 25° C and in a solvent

such as toluene, THF or dimethylformamide wherein R is a moiety of the following formula (III):



(b) Reaction of an alcohol of the formula RCH_2OH with sulfurylchloride of the formula SO_2Cl_2 in the presence of a base such as triethylamine or pyridine at a temperature of about -40° to 25° C in a solvent such as diethyl ether or methylene chloride to produce a chlorosulfate of the formula RCH_2OSO_2Cl .

The chlorosulfate of the formula RCH_2OSO_2Cl may then be reacted with an amine of the formula R_1NH_2 at a temperature of about 40° to 25° C in a solvent such as methylene chloride or acetonitrile to produce a compound of formula (I). The reaction conditions for (b) are also described by T. Tsuchiya et al. in Tet. Letters, No. 36, p. 3365 to 3368 (1978).

(c) Reaction of the chlorosulfate RCH_2OSO_2Cl with a metal azide such as sodium azide in a solvent such as methylene chloride or acetonitrile yields an azidosulfate of the formula $RCH_2OSO_2N_3$ as described by M. Hedayatullah in Tet. Lett. p. 2455-2458 (1975). The azidosulfate is then reduced to a compound of formula (I) wherein R_1 is hydrogen by catalytic hydrogenation, e.g. with a noble metal and H_2 or by heating with copper metal in a solvent such as methanol.

The starting materials of the formula RCH_2OH may be obtained commercially or as known in the art. For example, starting materials of the formula RCH_2OH wherein both R_2 and R_3 and R_4 and R_5 are identical and are of the formula (II) may be obtained by the method of R. F. Brady in Carbohydrate Research, Vol. 14, p. 35 to 40 (1970) or by reaction of the trimethylsilyl enol ether of a R_6COR_7 ketone or aldehyde with fructose at a temperature of about 25° C, in a solvent such a halocarbon, e.g. methylene chloride in the presence of a protic acid such as hydrochloric acid or a Lewis Acid such as zinc chloride. The trimethylsilyl enol ether reaction is described by G. L. Larson et al in J. Org. Chem. Volaa 38, No. 22, p. 3935 (1973).

Further, carboxylic acids and aldehydes of the formulae $RCOOH$ and $RCHO$ may be reduced to compounds of the formula RCH_2OH by standard reduction techniques, e.g. reaction with lithium aluminum hydride, sodium borohydride or

borane-THF complex in an inert solvent such a diglyme, THF or toluene at a temperature of about 0° to 100° C, e.g. as described by H.O. House in "Modern Synthetic Reactions", 2nd Ed., pages 45 to 144 (1972). In patients treated with topiramate as an adjunctive therapy in epilepsy (n=1319), mean weight loss of 4.6% of baseline weight was observed. The mean daily dosage of topiramate was 621.9 mg/day and the mean duration of dosing was 688.8 days. The mean decrease was 8.4% in the subset of subjects weighing >100 kg (n=127); these subjects had a mean daily dose of topiramate of 873.5 mg/day and a mean duration of dosing of 881.8 days. On topiramate treatment, there is gradual weight loss over time, with maintenance of the weight lost to 24 months of therapy; thus the mean percentage decrease in weight for all subjects (n=1319) was 4.6%, with similar weight loss maintained at one year (4.9%) and two years (4.5%) of treatment. This pattern is also seen in those patients with weight in excess of 100 kg at baseline (n=127), who lost a mean of 8.4% weight overall, with loss of 9.4% at one year and 9.9% at two years.

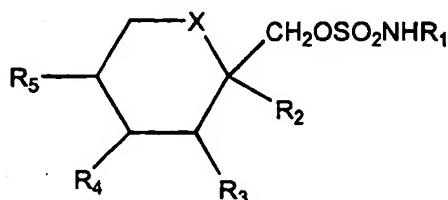
For maintaining weight loss, a compound of formula (I) may be employed at a daily dose in the range of about 100 mg to 400 mg, usually in two daily divided doses, for an average adult human. A unit dose would contain about 15 to 200 mg of the active ingredient.

To prepare the pharmaceutical compositions of this invention, one or more sulfamate compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral, by suppository, or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. Suppositories may be prepared, in which case

- cocoa butter could be used as the carrier. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable solutions may also be prepared in which case appropriate stabilizing agents may be employed. Topiramate is
- 5 currently available for oral administration in round tablets containing 25 mg, 100 mg or 200 mg of active agent. The tablets contain the following inactive ingredients: lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.
- 10 The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder injection, teaspoonful, suppository and the like from about 25 to about 200 mg of the active ingredient.

WHAT IS CLAIMED IS:

1. A method for maintaining weight loss comprising administering to such a mammal
 5 a therapeutically effective amount for treating such condition of a compound of the formula I:



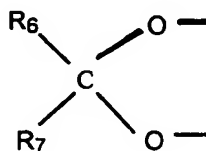
wherein

X is CH₂ or oxygen;

- 10 R₁ is hydrogen or alkyl; and

R₂, R₃, R₄ and R₅ are independently hydrogen or alkyl and, when X is CH₂, R₄ and R₅ may be alkene groups joined to form a benzene ring and, when X is oxygen, R₂ and R₃ and/or R₄ and R₅ together may be a methylenedioxy group of the following formula (II):

15



wherein

- R₆ and R₇ are the same or different and are hydrogen, lower alkyl or are alkyl and are
 20 joined to form a cyclopentyl or cyclohexyl ring.

2. The method of claim 1 wherein the compound of formula I is topiramate.
 3. The method of claim 1, wherein the therapeutically effective amount is of from about 100 to 400 mg/day.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/08442

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/255 A61K31/35 A61K31/7048 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, SCISEARCH, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	YORK D A (REPRINT) ET AL: "Effects of topiramate on high fat diet-induced obesity" FASEB JOURNAL, (15 MAR 2000) VOL. 14, NO. 4, PP. A431-A431. PUBLISHER: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998. ISSN: 0892-6638., XP000915192 PENNINGTON BIOMED RES CTR, BATON ROUGE, LA 70808 the whole document	1-3
X	WO 98 00130 A (ORTHO PHARMA CORP) 8 January 1998 (1998-01-08) cited in the application the whole document	1-3
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 August 2000

Date of mailing of the international search report

22/08/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818, Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hoff, P

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 00/08442

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>POTTER, DOREEN ET AL: "Sustained weight loss associated with 12-month topiramate therapy." EPILEPSIA, (1997) VOL. 38, NO. SUPPL. 8, PP. 97. MEETING INFO.: ANNUAL MEETING OF THE AMERICAN EPILEPSY SOCIETY BOSTON, MASSACHUSETTS, USA DECEMBER 7-10, 1997 AMERICAN EPILEPSY SOCIETY. , XP000923402 abstract 3.033</p> <p style="text-align: center;">---</p>	1-3
X	<p>ROSENFELD, WILLIAM E. (1) ET AL: "Topiramate and concomitant weight loss." EPILEPSIA, (1997) VOL. 38, NO. SUPPL. 8, PP. 98. MEETING INFO.: ANNUAL MEETING OF THE AMERICAN EPILEPSY SOCIETY BOSTON, MASSACHUSETTS, USA DECEMBER 7-10, 1997 AMERICAN EPILEPSY SOCIETY. , XP000923403 abstract 3.037</p> <p style="text-align: center;">---</p>	1-3
X	<p>PENOVICH, PATRICIA ET AL: "Weight loss in patients receiving topiramate for intractable epilepsy." NEUROLOGY, (1994) VOL. 44, NO. 4 SUPPL. 2, PP. A204-A205. MEETING INFO.: 46TH ANNUAL MEETING OF THE AMERICAN ACADEMY OF NEUROLOGY WASHINGTON, D.C., USA MAY 1-7, 1994 , XP000923409 abstract 309P</p> <p style="text-align: center;">---</p>	1-3
A	<p>US 4 513 006 A (MARYANOFF BRUCE E ET AL) 23 April 1985 (1985-04-23) cited in the application the whole document</p> <p style="text-align: center;">---</p>	1-3
A	<p>KYOWA HAKKO: "TOPIRAMATE" DRUGS OF THE FUTURE, ES, BARCELONA, vol. 21, no. 4, 1996, pages 463-465, XP002043895 ISSN: 0377-8282 the whole document</p> <p style="text-align: center;">-----</p>	1-3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/08442

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9800130 A	08-01-1998	AU 3957897 A CA 2258893 A CZ 9804278 A EP 0915697 A NO 986052 A ZA 9705772 A	21-01-1998 08-01-1998 11-08-1999 19-05-1999 23-02-1999 28-12-1998
US 4513006 A	23-04-1985	AT 36149 T AU 564842 B AU 3350484 A CA 1241951 A DE 3473143 D DK 198191 A,B, DK 198291 A DK 457784 A,B, EP 0138441 A ES 536225 D ES 8602634 A FI 843765 A,B, HU 36784 A,B IE 57684 B JP 1804249 C JP 5005824 B JP 60109558 A JP 5331132 A KR 9201775 B MX 9202630 A NO 843836 A,B, NZ 209494 A US 4582916 A ZA 8407550 A	15-08-1988 27-08-1987 04-04-1985 13-09-1988 08-09-1988 09-12-1991 09-12-1991 27-03-1985 24-04-1985 16-11-1985 16-03-1986 27-03-1985 28-10-1985 24-02-1993 26-11-1993 25-01-1993 15-06-1985 14-12-1993 02-03-1992 30-06-1992 27-03-1985 06-03-1987 15-04-1986 28-05-1986